

Applicant : Kalyan Handique et al.
Serial No. : 10/075,371
Filed : February 15, 2002
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Attorney Docket No.: 19662-030001

IN THE DRAWINGS

Marked-up versions of FIGs. 6 and 7 showing changes, follow this page; a replacement sheet is positioned after the last page of this amendment and response.



Fig. 6



Fig. 7

REMARKS

Applicants have considered the office action mailed September 13, 2006 in connection with the above-identified patent application.

Applicants point out to the Examiner that Applicants filed an Information Disclosure Statement and List of References Cited by Applicant on October 16, 2006, and request his consideration thereof at such time as he next acts on the instant application.

Applicants also reiterate their request, expressed in the Amendment and Response filed June 23, 2006, and again ask that the Office records be updated with the current attorney docket number (19662-030001) for the subject application.

Amendments to Specification

With the instant amendment and response, Applicants amend the title of the application to be more reflective of the subject matter claimed, utilizing language that can be found throughout the specification as filed, for example, at page 7, lines 12 – 13.

Applicants amend the specification to insert various description of robotic control, as found in a prior application the contents of which are incorporated by reference into the specification of the instant application, and as further discussed hereinbelow in connection with amendments to the drawings.

Applicants also amend the specification to correct various typographical errors, the nature of which would be clear to one of ordinary skill in the art.

No new matter is introduced by way of these amendments, and entry thereof is therefore requested.

Amendments to the Drawings (and accompanying description)

The Examiner has requested amendment to the drawings, specifically FIGs. 1 and 3, to indicate the “laboratory robot” recited in claim 44, and its disposition with respect to sample input and reagent input modules. Applicants thank the Examiner for drawing Applicants’ attention to this item and have proceeded as follows.

The instant application is a continuation-in-part of application serial no. 09/819,105 (now U.S. patent no. 7,010,391, hereinafter the '391 patent). The contents of this prior application are incorporated by reference into the specification of the instant application (see, *e.g.*, specification as filed, page 1, lines 5 – 9). Accordingly, since the specification of the prior application is a part of the specification of the instant application (via an incorporation by reference), Applicants can amend the specification of the instant application to include material present in the '391 patent without adding new matter (see, *e.g.*, 37 C.F.R. § 1.57(d, f), and MPEP § 608.01(p)). Accordingly, in addressing the Examiner's request, Applicants amend the specification (but not the drawings) as follows.

The reference to “laboratory robot 154” in connection with FIG. 3 is corrected to reference, instead, FIG. 1 (wherein item 154 is found).

FIG. 1 of the instant application is closely similar to FIG. 3A of the '391 patent. Items 122 and 123 in FIG. 1 of the instant application correspond respectively to items 22 (“three inlet ports”) and 23 (“micro-circuit”) of FIG. 3A of the '391 patent. Accordingly, Applicants amend the specification of the instant application to incorporate material descriptive of items 22 from the specification of the '391 patent (specifically at col. 28, lines 32 – 36, and lines 39 – 41).

Furthermore, item 131 in FIG. 1 of the instant application corresponds to items 31 (“robot control”) of FIG. 3A of the '391 patent. Accordingly, Applicants amend the specification of the instant application to incorporate material descriptive of item 31 from the specification of the '391 patent (specifically at col. 30, lines 29 – 33).

The foregoing amendments are, Applicants believe, the most conservative amendments that are consistent both with addressing minor discrepancies between the specification and the figures and the Examiner's request for clarification of the manner in which input modules are “structurally configured to accept material from laboratory robot 154”. With respect to the latter point, Applicants also draw the Examiner's attention to the specification of the '391 patent, for example at section 5.3.2.6 (“Micro-Droplet Metering Function”) (cols. 40 – 41 of the '391 patent, which, as discussed herein, is incorporated by reference into the instant application). Thus, Applicants respectfully submit that the instant application is complete as to a description

of how an input module is configured to accept material from a robot, either through the specific amendments herein, or via statements of incorporation by reference.¹

Applicants also refer the Examiner to other minor amendments to FIGs. 6 and 7 presented herein, to correct various clerical errors, the nature of which would be clear to one of ordinary skill in the art, and which are as follows.

FIG. 6 is amended herein to delete a second instance of reference numeral 400. Applicants respectfully point out that, as would be clear from the accompanying portion of the specification (see, *e.g.*, page 9, lines 26 – 31 of the instant application ([0060] of the publication of the instant application, U.S. Patent Application Publication No. 2002/0142471)) the reference numeral 400 refers to a space, as shown in both FIGs. 6 and 7. The instance of numeral 400 that points to a lower surface of member 900 in FIG. 6 as filed is thus clearly in error and is deleted herewith.

FIG. 7 has been amended herein to correct the reference numerals 936 and 913, to 136 and 931 respectively. The correction of such reference numerals is consistent with other drawings including, for example, FIG. 6, and the accompanying description found in the specification as filed (see, *e.g.*, page 9, line 26 – page 10, line 14 of the instant application ([0060] and [0061] of Patent Application Publication No. 2002/0142471)).

All of the foregoing amendments to the figures are therefore merely for completeness and consistency, and no new matter is introduced thereby.

Amendments to the Claims, and New Claims

Claim 32 is amended herein to recite various features of the several modules. Support for these amendments is found variously in the specification and figures as filed, for example as follows: enrichment module (*e.g.*, page 8, line 29 to page 9, line 4); microdroplet preparation module (*e.g.*, page 12, line 16 – 21); cell lysing module (*e.g.*, page 10, lines 14 – 15); mixing

¹ Applicants note that the Examiner has *not* characterized the items for which clarification is sought as “essential material”. Should he conclude that one or more of the items are essential material, Applicants remind him that essential material may be included via a statement of incorporation by reference where the reference is — as here — to another U.S. patent (see 37 C.F.R. § 1.57(c)).

module (*e.g.*, page 16, lines 28 – 31); and DNA manipulation module (*e.g.*, page 18, lines 29 – 30).

Claims 41 and 42 are amended to more particularly recite the invention, support for the amendments being found in the specification as filed at, *e.g.*, page 5, lines 5 – 6, and page 4, lines 22 – 26.

Claims 45 and 47 are amended to change their respective dependencies.

Claims 48 and 49 are amended herein to recite limitations of the sample and the enriched sample as found in the specification as filed at, *e.g.*, page 11, lines 5 – 10.

Applicants amend claim 50, to recite features of the flow-through member and the enrichment module, support for which can be found in the specification as filed at, *e.g.*, page 8, line 27 – page 9, line 4.

Claim 51 is amended to correct a syntactical error.

Applicants amend claim 54 herein to delete a term for which antecedent basis is lacking.

Claims 59 and 63 are amended to correct antecedent basis.

Claim 67 is amended to recite features of the sample, also found in claims 45 and 47.

Applicants amend claim 74 to recite aspects of the vent and valves, and also to correct antecedent basis for the term “mixing module”. Support for these amendments can be found in the specification as filed, for example at, respectively, page 19 lines 6 – 7, and 8 – 9.

Claim 76 is amended to recite operations of the DNA manipulation module, as recited in the specification as filed, at for example, page 18, line 31.

Applicants amend claim 77 to adjust its dependency, and further to recite computer control, as found in the specification as filed, at for example page 19, line 10.

Applicants amend claim 78 to adjust its dependency.

Applicants introduce new claims 79 and 80 to recite features of the substrate, as found in the specification as filed at, *e.g.*, page 6, lines 21 – 23, and page 7, lines 11 – 12.

Applicants further introduce new claims 81 – 83, to recite particles per volume of fluid ratios, support for which can be found in the specification as filed at, *e.g.*, page 11, lines 5 – 10.

Claim 84, reciting a microfluidic device, is also introduced herein, and is supported by the specification as filed, in for example FIG. 1, and accompanying description at, *e.g.*, page 4, lines 18 – 19.

Accordingly, the new and amended claims presented herein are supported by the specification as filed, and thereby introduce no new matter. Entry thereof is respectfully requested.

REJECTIONS OF THE CLAIMS

Rejections under 35 U.S.C. § 112 (¶ 2)

The Examiner has rejected claims 50 – 56, and 74 – 78 under 35 U.S.C. § 112 (second paragraph) as being incomplete for allegedly “omitting essential structural cooperative relationships of elements”.

In respect of claim 50, the Examiner asserts that it is “unclear as to how the flow-through member and enrichment chamber are fluidically connected.” With the instant amendments, Applicants amend claim 50 to recite that the enrichment chamber and flow-through member are adjacent, and further that “the enrichment module is configured to allow fluid of a particle-containing fluid to pass through the flow-through member thereby accumulating an enriched particle sample, comprising particles of the particle-containing fluid, in the enrichment chamber.”

Regarding claim 74, the Examiner alleges that “it is unclear as to how the vent, first valve and second valve are fluidically connected.” Applicants amend claim 74 herein to recite positive features of the vent and both the valves.

Applicants also thank the Examiner for pointing out the lack of antecedent basis for the term “mixing zone”, a matter that has been cured by the instant amendment, as discussed hereinabove.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 32 – 61, and 63 – 78, under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,664,104 to Pourahmadi, (“Pourahmadi”,

hereinafter), in view of U.S. Patent No. 6,130,098 to Handique (“Handique” hereinafter). Claim 62 is rejected as obvious over a combination of Pourahmadi, in view of Handique, and further in view of U.S. Patent No. 6,544,734 to Briscoe, *et al.*, (“Briscoe”, hereinafter). Applicants respectfully traverse the rejections.

The U.S. Patent and Trademark Office (“PTO”) bears the burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993). To establish a *prima facie* case, the PTO must satisfy three basic criteria, one of which is that the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Applicants respectfully submit that the Examiner has not satisfied the Office’s burden of establishing a *prima facie* case, at least because the combination of cited references fails to teach or disclose every element of Applicants’ claimed invention.

Applicants’ claim 32, from which all other claims depend directly or indirectly, recites a microfluidic device comprising a microfluidic network which itself comprises several modules — including at least an enrichment module configured to accept a particle-containing fluid sample, and to create an enriched sample therefrom and a cell lysing module configured to lyse a microdroplet of enriched sample — wherein the several modules are operatively connected by one or more channels, at least one module is isolatable by a valve, and at least one actuator is configured to move a fluid microdroplet from one module to another.

To summarize the basis of the Examiner’s rejection — at least with respect to claims 32, 49, 50, 53, 57 – 61, 63, 64, 66, 68, 69, 70, 72 – 74, and 76 — Pourahmadi teaches a microfluidic device comprising various elements including pneumatic fluid motive sources, and including certain elements that he concludes correspond to Applicants’ recited modules, but not a microdroplet preparation module (September 13, 2006 Office Action, at pages 4 – 5). Since, according to the Examiner, Handique discloses a system and methods for microdroplet preparation, including a thermopneumatic apparatus for facilitating fluid transport, “it would [therefore] have been obvious to a person of ordinary skill in the art to incorporate a

microdroplet preparation module with an associated actuator as claimed to facilitate sample fluid transport” (September 13, 2006 Office Action, at page 6).

First, Applicants respectfully point out that the supposed correspondence between Pourahmadi’s flow-through component 122 and Applicants’ enrichment module or zone (September 13, 2006 Office Action, at page 4) is incorrect.

Applicants’ claims recite a microfluidic device having an “enrichment module configured to accept a particle-containing fluid sample” and a “cell lysing module configured to lyse [a] microdroplet of enriched sample.” Thus, in Applicants’ claimed invention, an enrichment module acts to enrich a particle-containing sample, and it is the enriched sample that is subsequently lysed. (See also, *e.g.*, Applicants’ specification as filed, page 8, line 31 – page 9, line 2: “an enrichment module [156] receives a flow of particle-containing fluid ... and allows the fluid to pass through the zone while accumulating particles within the zone.”) Such a device is different from the system of Pourahmadi, in which a flow-through component operates to bind nucleic acid from a fluid sample after the sample has been lysed (see, *e.g.*, Pourahmadi, col. 9, lines 4 – 8).

Thus, the device of Pourahmadi is configured to lyse a fluid sample in a lysing chamber 119 (FIG. 2, and col. 8, lines 43 – 63, of Pourahmadi) *prior to* passing the lysed sample through the flow-through component 122. The lysing chamber of Pourahmadi is fitted with a filter to capture cells, spores, and microorganisms, and remove debris from the sample (col. 8, lines 60 – 63, of Pourahmadi). Thus, the device of Pourahmadi is configured differently from that recited in Applicants’ claims in that Pourahmadi’s device has a lysing chamber (119) that simultaneously performs a particle filtration role and is separate from a nucleic acid capture component (122). Applicants’ claims, by contrast, recite a microfluidic device having an enrichment module that concentrates particulate matter from the sample, and has a separate lysing module that acts on the concentrated particulate matter.

In sum, Pourahmadi does not teach at least the configuration of elements in Applicants’ claimed invention. The deficiencies of Pourahmadi are not provided by Handique, which does not describe an enrichment module, or teach methods for sample enrichment prior to lysing, in

microfluidic systems. Thus, the invention recited in the instant claims cannot be found in the cited references, either alone or in combination. Accordingly, for at least this reason, Applicants' claim 32 is not obvious over a combination of Pourahmadi and Handique.

Dependent claims are nonobvious under 35 U.S.C. § 103 "if the independent claims from which they depend are nonobvious." *In re Fine* 837 F.2d 1071; 5 USPQ.2d 1596; MPEP 2143.03. Thus, the specific rejections of dependent claims 33 – 48, 51, 52, 54 – 56, 62, 65, 67, 71, and 75 are mooted at least because a recitation of the independent claim from which they depend is not obvious over the cited references. Accordingly, Applicants respectfully submit that all of claims 33 – 61, and 63 – 75, 77 and 78, are also non-obvious over a combination of Pourahmadi and Handique.

Claim 62, which stands rejected over a combination of Pourahmadi, Handique, and Briscoe, is similarly non-obvious, at least for the following reason. Claim 62 recites a microfluidic device having the elements recited in claim 32, and having additionally a lysing mechanism that comprises one or more electrodes, configured to deliver a pulsed electric field to a microdroplet containing cells. Notwithstanding the fact that neither of Handique, Pourahmadi, nor Briscoe teaches lysing of microdroplets of fluid, Briscoe does not teach or disclose the enrichment module and lysing chamber, configured as recited in Applicants' claims, that are similarly absent from Pourahmadi and Handique. In fact, Briscoe discloses a system in which lysing of a sample occurs prior to separation of DNA from the lysed sample, but wherein there is no enrichment (see, *e.g.*, Briscoe, FIG. 1, and col. 3, lines 3 – 16). Accordingly, claim 62 is not obvious over a combination of Handique, Pourahmadi, and Briscoe.

Although the foregoing distinctions between the claimed invention and the cited references transcend any considerations of motivation to combine or reasonable expectation of success in combining the references, Applicants also take this opportunity to further rebut the Examiner's reasoning in respect of motivation to combine the teachings of the art (reasoning which, of course, was predicated on a conclusion that the references in combination did disclose every element of Applicants' claimed invention, a conclusion that has now been vitiated by the foregoing amendments and remarks).

In essence, the Examiner has alleged that one of ordinary skill in the art would have had a reasonable expectation that the microfluidic manipulation methods taught by Handique could be successfully combined with a continuous flow microfluidic system of Pourahmadi. In particular, the Examiner references the disclosure of an actuator in Handique and alleges that “it would have been obvious to a person of ordinary skill in the art to incorporate a microdroplet preparation module with an associated actuator as claimed to facilitate sample fluid transport”, (September 13, 2006 Office Action, at page 6). Applicants respectfully disagree because the actuator of Handique is configured to move a microdroplet, whereas the device of Pourahmadi is configured to accept samples on a continuous-flow model, and explicitly teaches away from using “bolus-based” processes (see, *e.g.*, Pourahmadi, Background Section, and col. 5, lines 8 – 17). Without a specific teaching that the actuators of Handique can be configured to move continuous volumes of fluid, and *vice versa*, one of ordinary skill in the art would simply not have expected to be able to use the actuators of Handique with Pourahmadi’s device.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the subject application is in good and proper order for allowance. Withdrawal of the Examiner’s rejections and early notification to this effect are earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 839-5005.

[SIGNATURE BLOCK AND FEE AUTHORIZATION ON FOLLOWING SHEET]

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No fee is believed owed in connection with filing of the instant amendment and response, other than the fee for additional claims, and the extension of time fee, as separately authorized on even date herewith. However, should the Commissioner determine otherwise, the Commissioner is authorized to charge any underpayment or credit any overpayment to Fish & Richardson P.C. Deposit Account No. 06-1050 (ref. No. 19662-030001) for the appropriate amount. A copy of this sheet is attached.

Respectfully submitted,

Date: 03/13/07

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